ABSTRACT

Camptothecin (CPT) is a highly cytotoxic natural alkaloid that has not yet found use as chemotherapeutic agent due to its poor solubility in water/biocompatible solvents and chemical instability at alkaline pH. Hence effective delivery systems are necessitated for the administration of CPT. The main objective of the present study was to develop and characterize CPT loaded microemulsions, for the passive/active targeted delivery of the CPT to the breast cancer tissues.

Based on the pseudoternary phase diagrams camptothecin loaded microemulsions (CPT MEs), camptothecin loaded magnetic microemulsions (CPT MMEs) and camptothecin loaded polymer stabilized microemulsions (CPT PSMEs) were prepared. Mixtures of benzyl alcohol: captex300 (3/1) and Capmul MCM were used as oil phase. Vitamin E TPGS: tween80 (1:2) was selected as S_mix for CPT MEs/CPT MMEs. Whereas Solutol HS 15 and Simulsol P 23 (1:2) were selected as S_mix for the polymer stabilized microemulsion (CPT PSME). The selected compositions from the phase diagrams were subjected to thermodynamic stability stress.

The formulated microemulsions (CPT MEs, CPT MMEs and CPT PSMEs) were characterized for its globule size, pH, refractive index, surface morphology, magnetic susceptibility, effect of droplet size in plasma and evaluated for its in-vitro and in-vivo targeting potential, in-vitro drug release, in-vitro haemolytic potential, cytotoxicity, genotoxicity, in-vivo biodistribution and lactone ring stability.
The optimized microemulsions (CPT MEs, CPT MMEs and CPT PSMEs) were acidic in nature, had spherical oil droplets with a uniform droplet size of 12-31 nm and charge of -3.39 to 3.91 mV. The amount of camptothecin present in the formulations was found to be in the range of 331-419 µg/mL in CPT MEs and CPT MMEs and 114.55-193.81 µg/mL in CPT PSMEs. In vitro release studies showed a sustained release of camptothecin for 24 h. The magnetic susceptibility of the CPT MMEs was in the range of 52-56 × 10^{-6}. The acceptable level of haemolytic activity (≤20%) showed by the formulated microemulsions indicates the safety of formulations. CPT MEs, CPT MMEs and CPT PSMEs showed significant (p<0.05) cytotoxicity against MCF-7 cells in comparison to pure drug with low DNA damage in lymphocytes. Targeting potential of developed formulations was documented in 4T1 breast cancer induced BALB/c mice. In vivo biodistribution studies showed effective the active targeting/passive targeting of camptothecin to the breast cancer than CPT solution. Lactone ring stability studies of developed formulations indicate that around 80% of the CPT in bioactive lactone form in the physiological pH.

The results of the present study conclude that the developed camptothecin loaded microemulsions may act as a promising nanocarrier system for efficient parenteral targeted delivery of CPT for breast cancer tissues with better circulatory effect.